1,090,340

PATENT SPECIFICATION

NO DRAWINGS

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COMPLETE SPECIFICATION

Dentrifice Composition

We, WARNER-LAMBERT PHARMACEUTICAL COMPANY, a Corporation organized under the laws of the State of Delaware, United States of America, of 201 Tabor Road, Morris Plains, State of New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to novel dentifrice compositions and to methods for their preparation. More particularly, this invention relates to dentifrice compositions for use in rehardening soft tooth enamel.

Dental enamel may be defined as a crystalline substance having a characteristic X-ray diffraction pattern practically identical with that of bone, dentin and certain synthetic or inorganic minerals such as fluoroapatite. On the basis of these X-ray findings substances having the characteristic X-ray diffraction pattern as that produced by dental enamel have been included in the general class "apatites". This general class, however, refers only to the particular atomic pattern or arrangement of crystal lattice and not to any consistency of the chemical composition which has been found to be capable of being ultimately expressed in a ratio of P_2O_5-CaO-H_2O. Dental enamel, or as it is sometimes called "hydroxyapatite" can best be expressed by the formula:

$$[Ca_9(PO_4)_6Ca(OH)_2]$$

in which the Ca/P ratio is theoretically 1.67. It is recognized that this formula is merely an expression of convenience and does not necessarily indicate the true state of the combination of elements present in dental enamel.

Since the chemistry of hydroxyapatite is directly applicable to that of dental enamel, it is evident that dental enamel allows for very interesting possibilities in the way of chemical reactions. For example, just as hydroxyapatite will react with solutions of calcium fluoride to form the relatively insoluble fluoroapatite, so does the possibility exist for similar addition and exchange reactions between the constituent ions of the dental enamel with other ions maintained in contact with the enamel surface. It is known, for example, that the enamel surfaces of teeth are normally in equilibrium with the components of saliva and especially with the calcium and phosphate ions present therein. A continuous exchange of these ions between the enamel surface and the saliva has been confirmed by studies with radioactive tracers such as that presented by Barum and Armstrong in Amer. J. Physiol. 135: 478—484 (1942) and by Sognnaes and Shaw in J. Am. Dent. Assoc., 44: 489—505 (1952).

Enamel softening and rehardening studies or the process involving ion exchange between the tooth surface and the saliva have been the focus of increased interest since the observations of Head (Dent. Cos. 52, 46—48, (1910)) who described the invivo repair of etched enamel surfaces by saliva. Based on these observations, various attempts have been made to inhibit formation of dental caries by utilizing the chemical reactivity of ions of constituents forming the dental enamel with those ions in the saliva. For example, Nebergall in U.S. Pat. No. 2,876,166, discloses that the combination of a soluble fluoride in certain calcium phosphates may be used in dentrifrices for the purpose of inhibiting the solubility of dental enamel. Ruthrauff, in U.S. Pat. Nos. 1,222,144 and 1,225,362, teaches the incorporation of soluble calcium salts in the acetate form in dentrifrices for the purpose of depositing calcium ions on the teeth so as to repair the teeth by building up the enamel coating. To date, however, these various attempts at remineralizing the enamel coating have met with limited success

[Price

and have proven of little or no utility in rehardening softened tooth enamel.

Most previous attempts at rehardening softened dental enable involved the use of saliva. When attempts were made to protect teeth by exposure to artificially prepared solutions such as solutions of fluorides or salts of calcium and/or phosphates, the solutions were undersaturated or at best saturated, with respect to the mineral phase of the tooth enamel. Under such conditions, only ion exchange takes place between the minerals present in saliva and the minerals of the tooth enamel.

The present invention, however, provides compositions suitable for rehardening softened dental enamel comprising compositions which yield, on contact with saliva, supersaturated solutions which not only allow exchange of ions between the minerals of the saliva and the minerals of the enamel but also which add to or replace missing ions from the mineral structure of teeth. The components of the present invention reharden softened dental enamel by double decomposition reactions. Solutions which may be used experimentally to determine *in vitro* rehardening may be prepared as follows:

(1) By dissolving hydroxyapatite or dicalcium phosphate in acids and then neutralizing the solution, after the addition of fluoride ions for optimal results.

(2) By mixing a water solution of a soluble calcium salt with a water solution of a soluble phosphate salt, also preferably in the presence of fluoride ions.

(3) By adding a solid mixture of a water soluble calcium salt with a water soluble phosphates salt to water or saliva, along with some soluble fluoride salt.

In each of the above instances, it is generally desirable to have a Ca/P molar ratio of 1.67 as in the hydroxyapatite of enamel but wide variations are possible.

It has also been found that the presence of sodium chloride greatly enhances the stability of supersaturated solutions formed by the dental compositions according to this invention. Most rehardening solutions lose their effectiveness after several hours, but when these same solutions contain sodium chloride, the rehardening effectiveness is prolonged for at least two weeks after preparation. In addition, the presence of sodium chloride permits higher concentrations of calcium and phosphate ions to be used as well as allowing wider variations in the pH of the solution.

It is a primary object of this invention to provide dental compositions which prevent softening of dental enamel and which reharden softened enamel through recalcification.

It is also an object of this invention to provide a dental composition which forms supersaturated solution of a calcium phosphate compound formed by the reaction of water soluble calcium and phosphate salts in a medium such as saliva or water at slightly alkaline pH while in the presence of dental enamel and thereby rehardening or superhardening the enamel through recalcification.

It is a further object of this invention to provide a dental composition which forms a supersaturated solution of calcium ions and phosphate ions in the presence of saliva and which contains stabilizing effective amounts of sodium chloride ions and also a soluble fluoride salt for the purpose of preventing softening of dental enamel.

These and other objects will become apparent from the following detailed description.

According to the present invention, the present compositions comprise mixtures of water soluble calcium salt and a water soluble phosphate salts which when brought into contact with slightly alkaline aqueous solutions will form a supersaturated solution such that the calcium and phosphate ions will form apatite mineral in dental enamel thereby rehardening the tooth structure through recalcification. Since fluoride ions generally improve the rehardening process, a soluble fluoride salt is a part of the dentifrice composition. Compositions of the present invention also contain sodium chloride which clearly improves the rehardening characteristics by lengthening the stability of the supersaturated solution formed in the presence of saliva and by increasing the rate of rehardening of the tooth structure.

In carrying out the experimental work which led to the present invention, excised teeth obtained from a dental surgeon and void of extraneous tissue were stored after extraction in water containing small amounts of thymol. The roots of the teeth were removed subsequently and the crowns are mounted in 63° C. melting point wax supported in an acrylic cylinder with the buccal surface horizontal. The enamel surface of the tooth is ground plane and polished with 4/0 emery paper to provide a horizontal surface on each crown. Hardness measurements are then made with a Kentron microhardness tester using a 500 gram weight and a Knoop indenter. The hardness tests are taken five times on the plane surface of the crown thereby avoiding the hazard of curvature influencing the hardness readings. These hardness determinations were taken as more fully described in the articles of Caldwell, et al., J. Dent. Res., 36:732 (1957); by Newbrun et al., J. Dent. Res., 38:293 (1959) and by Newburn et al, Aust, Dent. Journal, (August, 1960).

After the hardness measurements have been made upon the horizontal plane surfaces of the polished teeth, the dental enamel is softened with 0.001 M acetic acid buffer

adjusted to pH 5.5 with potassium hydroxide. One hundred ml. of the adjusted acid buffer are preferably employed in each experiment for periods from about 2 to about 14 hours while at a temperature of about 37° C. After the tooth has been softened, hardness measurements are taken on a horizontal surface in the manner previously described. Five indentations are made for each determination and the hardness is expressed as an average Knoop Hardness Number (KHN).

The softened teeth are taken after the hardness determinations and placed in the rehardening solution where they are maintained at 37° C. without stirring. At various time intervals, the teeth may be removed to fresh solutions during which time hardness measurements are taken.

The water soluble calcium salts which are usefully employed in the preparation of the present rehardening compositions include compounds such as, for example, calcium acetate, calcium gluconate, calcium lactobionate, and calcium chloride. Useful phosphate salts are exemplified by water soluble sodium phosphates, water soluble ammonium phosphates, water soluble potassium phosphates, and water soluble mono-calcium phosphates while the soluble fluoride salts include materials such as sodium fluoride, potassium fluoride, and calcium fluoride. These various water soluble salts may be used individually or in any combination in preparation of the present tooth rehardening composition.

The sodium chloride which is added to the tooth rehardening composition is desirably added as a solution isotomic to body fluids such as, for example, one having from a 0.14 molar to a 0.18 molar sodium chloride concentration but lower concentrations of non-isotonic solutions are also effectively employed down to 0.01 M. By employing effective amounts of these sodium chloride solutions in the rehardening composition, it is found that the rate of rehardening increases to as great as twice that of a solution free of sodium chloride. It is also found that a higher concentration of calcium and phosphate ions may result in the supersaturated solution containing sodium chloride ions.

The inclusion of sodium chloride in the rehardening dental composition of the present invention greatly improves the rehardening characteristics. The rate of rehardening of the dental enamel is found to be increased from an average of 40 KHN to 60 KHN in two hours.

Preparation A

Ingredient	Parts by Weight
Gum Base	25
Corn Syrup	12.5
Sucrose	57.53
Calcium gluconate	3.2
Monocalcium phosphate	.77
Flavors	1

All the corn syrup which is to be initially incorporated into the gum base is pre-mixed with the mono calcium phosphate. A premix is next prepared by blending the calcium gluconate with the sucrose. The gum batch is then prepared in the normal way with the gum base being blended with the corn syrup pre-mix in a gum kettle. Thereafter, the sucrose, flavoring and any remaining corn syrup is added and thoroughly mixed with the gum base from which slabs of chewing gum are prepared. Chewing gum so prepared is found useful in rehardening softened teeth.

Preparation B

The procedure of Preparation A is repeated with the further addition of 0.4 milligrams of calcium fluoride for each 3 grams of slab chewing gum produced. The composition so prepared proves to be more effective in rehardening softened teeth than the composition of Preparation A.

The following Example illustrates a composition according to the present invention.

EXAMPLE.

The procedure of Preparation A is repeated with the further addition of 0.4 milligrams of sodium fluoride and 90 milligrams of 0.16 M sodium chloride solutions for each 3 grams of gum. The composition so prepared proves to be more effective in rehardening softened teeth than the composition of Preparation A and about equally as effective as the composition of Preparation B over greatly extended periods of use.

Among the dental compositions within the purview of this invention are those employing suitable carriers such as mouth washes, toothpastes, toothpowders and troches. Preferably, however, the composition is in the form of a confectionery containing from 1% to 10% by weight of active ingredients and chewing gum and chewable confection compositions are most desirably employed to controllably release the mineral ions while in contact with the tooth surfaces. It is also recognized, however, that dry powder formulation may be prepared according to the present invention for oral application without a carrier. Such powder formulations may be formed into tablets and taken orally or added directly to water just prior to use.

WHAT WE CLAIM IS:—

1. A dentrifrice composition effective is rehardening softened dental enamel which comprises

(a) a soluble fluoride salt,
(b) a soluble calcium salt,
(c) a soluble phosphate salt, and
(d) sodium chloride,

wherein the calcium and phosphate salts are present in amounts sufficient to react in saliva to form a super-saturated solution of an

apatite mineral, and the sodium chloride is present in amount sufficient to stabilize said supersaturated solution.

2. A composition according to claim 1, in the form of confectionery containing from 1% to 10% by weight of a composition comprising (1) potassium fluoride, sodium fluoride or calcium fluoride; (2) calcium acetate, calcium gluconate, calcium lactobionate or calcium chloride (3) a soluble sodium phosphate, a soluble ammonium phosphate, a soluble potassium phosphate or a soluble monocalcium phosphate and (4) a stabilizing amount of 0.14 to 0.18 molar sodium chloride solution.

3. A composition according to claim 2 wherein the confectionery is chewing gum.

4. A dentifrice composition effective in rehardening dental enamel substantially as described herein with particular reference to the Example herein.

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